EXHIBIT 17

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
(b) (6)

******Pre-decisional Agency Information******

Memorandum

Date: March 29, 2016

To: (b) (6)
(b) (6) (b) (6)

From: (b) (6)

Subject: Labeling comments for NDA 20687/S-20
MIFEPREX (mifepristone) tablets

This consult review is in response to (b) (6) consult request dated July 29, 2015 for review of draft labeling for MIFEPREX (mifepristone) tablets. (b) (6) reviewed the proposed substantially complete version of the PI sent via email on March 10, 2016. Our comments on the PI are included directly on the attached copy of the labeling.

Our review of the Medication Guide will be conducted jointly with the (b) (6) and filed under separate cover.

(b) (6) appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact (b) (6).

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

(b) (6)

03/29/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

(b) (6) **LABELING REVIEW**

Date:	March 21, 2016
To:	(b) (6) (b) (6) ((b) (6)
Through:	(b) (6) Labeling (b) (6) ((b) (6) (b) (6) Labeling (b) (6) ((b) (6)
From:	(b) (6) Labeling Reviewer (b) (6) ((b) (6) (b) (6) Regulatory Review Officer (b) (6) ((b) (6)
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Mifeprex (mifepristone)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 020687
Supplement Number:	0-20
Applicant:	Danco Laboratories, LLC (Danco)

1 INTRODUCTION

On May 28, 2015, Danco submitted for the Agency's review a Prior Approval Supplement Application (Supplement 020) for Mifeprex (mifepristone) tablets, 200mg, for oral use. This submission includes, but is not limited to, proposed changes in the Prescribing Information (PI) based on the Physician Labeling Rule (PLR). Mifeprex (mifepristone) is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

This collaborative review is written by the [redacted] and the [redacted] in response to a request by the [redacted] on February 19, 2016, and July 29, 2015, respectively, for [redacted] and [redacted] to review the Applicant's proposed MG for Mifeprex (mifepristone) Tablets, 200mg.

2 MATERIAL REVIEWED

- Draft Mifeprex (mifepristone) tablets, 200mg, for oral use MG received on May 28, 2015, revised by the Review Division throughout the review cycle, and received by [redacted] on March 9, 2016.
- Draft Mifeprex (mifepristone) tablets, 200mg, for oral use MG received on May 28, 2015, revised by the Review Division throughout the review cycle, and received by [redacted] on March 17, 2016.
- Draft Mifeprex (mifepristone) tablets, 200mg, for oral use Prescribing Information (PI) received on May 28, 2015, revised by the Review Division throughout the review cycle, and received by [redacted] on March 9, 2016.
- Draft Mifeprex (mifepristone) tablets, 200mg, for oral use Prescribing Information (PI) received on May 28, 2015, revised by the Review Division throughout the review cycle, and received by [redacted] on March 10, 2016.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Ariel font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy (b) (6) and (b) (6) on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult (b) (6) and (b) (6) regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

(b) (6)

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505(b)(2) ASSESSMENT

Application Information		
NDA # 20687	NDA Supplement #: S- 020	Efficacy Supplement Type SE- 2
Proprietary Name: Mifeprex Established/Proper Name: mifepristone Dosage Form: tablet Strengths: 200 mcg		
Applicant: Danco Laboratories, LLC		
Date of Receipt: May 29, 2015		
PDUFA Goal Date: March 29, 2016	Action Goal Date (if different):	
(b) (6)		
Proposed Indication(s): Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	Indications and Usage Dosage and Administration Warnings and Precautions Adverse Reactions Clinical Studies

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The drug product used in the cited literature is the applicant's approved drug product.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

NDA 020687 Mifeprex (mifepristone) Tablets

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☒

The studies described in the literature used the applicant's approved drug product, mifepristone 200 mcg, but the applicant did not conduct the studies and does not own or have right of reference to the studies/specific data described in the literature submitted.

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

(b) (6)

03/29/2016

LABEL AND LABELING REVIEW

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Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 29, 2016
Requesting Office or Division:	(b) (6) ((b) (6)
Application Type and Number:	NDA 20687/S-020
Product Name and Strength:	Mifeprex (mifepristone) Tablets 200 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Danco Laboratories, LLC
Submission Date:	May 28, 2015
(b) (6) **#:**	2015-1720
(b) (6)	(b) (6)
(b) (6)	
(b) (6)	

1 REASON FOR REVIEW

This review responds to a request from the (b) (6) (b) (6) to evaluate the proposed changes in dosage for the Mifeprex Prescribing Information (PI), submitted to efficacy supplement NDA 20687/S-020, for vulnerabilities that may contribute to medication errors.

In addition to being a PLR conversion, this efficacy supplement, S-020, proposes changes to the dosage and administration instructions for this product. The approved dosage is three 200 mg tablets (600 mg) of Mifeprex in a single oral dose on Day 1, followed by the patient returning to the health care provider two days after ingesting Mifeprex to take two 200 mg (400 mg) of misoprostol orally for medical termination of intrauterine pregnancy through (b) (4) days gestation. Danco Laboratories, LLC is now proposing (b) (4)

(b) (4) is for pregnancies through (b) (4) days gestation: 200 mg Mifeprex on Day 1, followed on Day 2 or Day 3 by 800 mcg buccal misoprostol (minimum 24-hour interval between Mifeprex and misoprostol).

(b) (4)

Additionally, the dosage and administration section of the prescribing information will no longer require that mifepristone be administered under the supervision of a licensed health care provider and will allow prescribers to dispense mifepristone to patients to self-administer outside of a supervised setting.

The currently marketed packaging configuration for Mifeprex is a blister pack containing three 200 mg tablets. The Applicant also submitted a manufacturing supplement, S-021, for a new single tablet blister pack configuration to support the proposed change in dosage. Danco has indicated that the single tablet blister pack will (b) (4) (b) (6) is reviewing the manufacturing supplement under separate cover (see (b) (6) (b) (6) # 2015-2527).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Previous (b) (6) Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed revisions to the prescribing information (PI) noted that Mifeprex and the subsequent dose of misoprostol will no longer require administration under the supervision of a licensed health care provider. The labeling changes will allow prescribers to dispense mifepristone directly to patients to self-administer outside of a supervised setting. Patients will also be allowed to self-administer their subsequent dose of misoprostol outside of a supervised setting. In addition, Danco proposes a new dosing regimen of one 200 mg Mifeprex tablet administered on day one followed on day 2 or day 3 by 800 mcg misoprostol administered buccally. The labeling will also include a medication guide which will be dispensed to each patient and there will be a REMS in place which will include a requirement for patient counseling. (b) (6) finds the content changes to the Dosage and Administration section acceptable and is working with the Division on the presentation of the (b) (4) in the Dosage and Administration section.

We also note that the newly proposed dosage regimen (b) (4) is not supported by the currently marketed blister pack, which contains three 200 mg tablets of Mifeprex. We are concerned that the use of the approved three tablet packaging configuration for patients prescribed (b) (4) may lead to medication errors. The currently marketed blister pack is not perforated to allow for easy removal of a single tablet for dispensing. Additionally, the currently marketed blister pack does not adequately label each individual tablet with identifying information to ensure safe use of the product. Dispensing a single tablet from the three tablet blister pack would not allow individual tablets to be labeled with the product name, strength, lot number or expiration date. If a provider did attempt to dispense a single tablet from the currently marketed blister pack, this may result in confusion of Mifeprex with other medications due to the lack of identifying information.

Additionally, prescribers may dispense the entire blister pack, which contains three 200 mg Mifeprex tablets, to patients who are only supposed to take one tablet. This introduces the risk

for patients to take all three 200 mg Mifeprex tablets at once (overdose). We recognize that if a patient did take all three tablets at once, it would be consistent with current practice, which allows for 600 mg of Mifeprex on day 1 through through (b) (4) days gestation. However, if this is followed by 800 mcg buccal misoprostol on day 3 instead of the currently approved 400 mcg oral misoprostol, it is unclear what the negative clinical consequences will be for the patient. We also cannot exclude the possibility that patients may reserve the extra two tablets for self-treatment or treatment of others at a later date. While such a practice would constitute intentional misuse of the product, this is a current public health concern that should be considered.

The Applicant submitted supplement 021, which proposes a new single tablet, 200 mg Mifeprex, blister pack. The newly proposed packaging configuration appears to be a reasonable approach for addressing the safety concerns we have outlined above. Coordinated timing for approval of both supplements 020 and 021 simultaneously or ensuring that an approval action is taken on supplement 021 prior to supplement 020 will help to ensure that an appropriate packaging configuration is available to support the safe use of the product for the dosage regimen proposed in supplement 020. We consider this especially important given that mifepristone no longer has to be administered under the supervision of a licensed health care provider and will be dispensed to patients to self-administer outside of a supervised setting.

4 CONCLUSIONS AND RECOMMENDATIONS FOR THE DIVISION

(b) (6) finds the proposed labeling changes in the prescribing information acceptable and is working with the Division during labeling meetings to discuss the presentation of the dosing option statements in the Dosage and Administration section. However, in the course of our review we determined the currently approved three tablet blister packaging configuration will not support the safe use of the product for the dosage regimen proposed in supplement 020. We recommend the Division coordinates the timing for approval of both supplements 020 and 021 to ensure that an appropriate packaging configuration is available to support the safe use of the product for the dosage regimen proposed in supplement 020. If supplement 021 cannot be approved prior to or at the same time as approval for supplement 020 and the Division determines that the public health benefits for approval of the new dosage regimen outweigh the safety concerns we have identified, then additional labeling mitigations may be needed to minimize the risk for medication error. (b) (6) should be consulted to provide additional recommendations in that circumstance.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mifeprex that Danco Laboratories LLC submitted on May 28, 2015.

Table 2. Relevant Product Information for Mifeprex	
Initial Approval Date	September 28, 2000
Active Ingredient	mifepristone
Indication	Medical termination of intrauterine pregnancy through (b) (4) days gestation.
Route of Administration	Oral
Dosage Form	Tablets
Strength	200 mg
Dose and Frequency	200 mg (b) (4)
How Supplied/ Container Closure	Blister pack (b) (4)
Storage	25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

APPENDIX B. PREVIOUS (b) (6) REVIEWS

B.1 Methods

On October 15, 2015, we searched the L:drive and AIMS using the terms, Mifeprex and mifepristone to identify reviews previously performed by (b) (6)

B.2 Results

Our search did not identify any previous reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 15, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care, Community and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Mifeprex

D.2 Results

One pertinent article was found in the July 24, 2002 edition of Medication Safety Alert which described a case involving a 59 year old male with a meningioma, who received a prescription for an off label use for mifepristone 200 mg po daily. The prescription was written by a provider who was unaware of the requirement to sign and return a prescriber's agreement. The prescription was filled incorrectly in a community pharmacy with misoprostol 200 mcg tablets.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on August 11, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[1]

Table 3: FAERS Search Strategy	
Date of Search	**August 11, 2015**
Product	Mifeprex
Event (MedDRA Terms)	(b) (6) **Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search identified three cases, none of which, described errors relevant for this review.

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

E.3 List of FAERS Case Numbers

N/A

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX F. Other Sources
N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Mifeprex labeling submitted by Danco Laboratories on July 16 2015.

- Package insert (no image)
- Medication Guide (no image)

(b) (4)

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

01/29/2016

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(b) (6)

01/29/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 020687/S- 020

Application Type: Efficacy Supplement

Drug Name(s)/Dosage Form(s): Mifeprex (mifepristone) Tablets

Applicant: Danco Laboratories, LLC

Receipt Date: May 29, 2015

Goal Date: March 29, 2016

1. Regulatory History and Applicant's Main Proposals

Mifeprex is currently approved and indicated for the medical termination of intrauterine pregnancy through 49 days' gestation. Danco Laboratories, LLC, submitted an efficacy supplement proposing modifications to their approved application. The revisions to the dosing regimen and extended gestational age are consistent with current clinical practice in the US and elsewhere. The goal date for the supplement is March 29, 2016.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

A SRPI format deficiency was identified in the review of this PI. See Section 4 of this review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

NO 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *Change will be made to the label during labeling negotiations.*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

Selected Requirements of Prescribing Information

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

YES 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

YES 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

YES 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

APPEARS THIS WAY ON ORIGINAL

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

APPEARS THIS WAY ON ORIGINAL

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

Selected Requirements of Prescribing Information

YES 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

APPEARS THIS WAY ON ORIGINAL

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

(b) (6)

12/02/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)
(b) (6)

Pharmacovigilance Review

Date:	November 16, 2015
Reviewer:	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
Product Names:	Mifeprex (mifepristone) and Cytotec (misoprostol)
Subject:	Uterine rupture
Application Type/Number:	NDA 020687 and NDA 019268
Submission Number:	Supplement-20 (for Mifeprex, NDA 20687)
Applicant/Sponsor:	Danco Laboratories, LLC and GD Searle, LLC
(b) (6) (b) (6) **#:**	2015-2270

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) for reports of uterine rupture with mifepristone alone, misoprostol alone, or both, with special interest in cases occurring in women ≤ 10 weeks pregnant (≤ 70 days). The [redacted] consulted the [redacted] as part of their review of an efficacy supplement submitted by Danco Laboratories, LLC, proposing labeling revisions for Mifeprex (mifepristone). These labeling revisions reflect established medical practice in regards to medical termination of pregnancy, and include changes to the eligible gestational age and [redacted] dosing regimen.

The FAERS search retrieved 80 cases of uterine rupture, with 77 citing misoprostol use alone and 3 citing both mifepristone and misoprostol use. Vaginal administration of misoprostol was documented in the majority of the cases. Twenty-five of the 80 cases originated in the published medical literature.

Cases were also assessed for other risk factors that could have contributed to uterine rupture. The majority noted at least one additional potential risk factor, with a history of at least one previous c-section, or the use of additional uterotonic drugs (e.g. oxytocin or dinoprostone), being the most commonly reported. The use of misoprostol during the 3rd trimester for the induction of labor, cervical ripening, or both, in women that had at least one previous c-section, was also documented in many cases.

The majority of the FAERS cases either occurred in the 3rd trimester of pregnancy, or did not report gestational age. Thirty-two of the 39 cases identified during the 3rd trimester noted vaginal misoprostol use. In the cases where the gestational age was not reported, it is likely that most of these cases occurred during the 2nd or 3rd trimester as many noted the induction of labor as the reason for misoprostol use. Two of the 80 cases (2.5%) reported uterine rupture within the first 10 weeks of pregnancy; however, if the cases without gestation age are not included as 2nd or 3rd trimester exposures despite the noted reason for use, the percentage increases to approximately 4%. Regardless of the approach, uterine rupture associated with the use of mifepristone alone, misoprostol alone, or both, is likely a rare event in the 1st trimester.

Two cases of uterine rupture were reported within the first 10 weeks of pregnancy. In both cases, misoprostol alone was utilized for termination of pregnancy. The first case provided minimal information other than documentation of a 5 week gestation, and an ultrasound noting "an important uterine separation" during an unspecified time after misoprostol (route not specified) administration. The remaining case was also a published case report in which uterine rupture was documented as occurring approximately 2.5 hours after 800 mcg of misoprostol was administered vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was 8 weeks and 2 days pregnant, had a history of a prior c-section, and was of advanced maternal age.

In conclusion, a review of the FAERS cases did identify cases of uterine rupture with the use of misoprostol alone, and with the use of mifepristone in combination with misoprostol. No cases of uterine rupture were reported with mifepristone use alone. While two cases of uterine rupture with misoprostol for the termination of pregnancy were reported in the ≤ 10 weeks gestation group, the vast majority of the cases documented uterine rupture in the 3rd trimester of pregnancy with vaginal misoprostol use alone for the induction of labor.

1 INTRODUCTION

Danco Laboratories, LLC submitted an efficacy supplement on May 28, 2015, proposing labeling revisions for Mifeprex (mifepristone). These labeling revisions reflect established medical practice in regards to medical termination of pregnancy, and include changes to the eligible gestation age and [redacted] dosing regimen, and are further described below.

> *Current indication:* medical termination of pregnancy through 49 days gestation
> *Current dosing/administration regimen:* 600 mg of mifepristone orally on day 1, followed by 400 mcg of misoprostol orally on day 3 (for pregnancies up to 49 days gestation)
>
> *Proposed* [redacted] *indication:* medical termination of pregnancy through [redacted] days gestation
> *Proposed* [redacted] *dosing/administration regimen:* 200 mg of mifepristone orally on day 1, followed by 800 mcg of misoprostol buccally on day 2 or 3 [redacted] for pregnancies up to [redacted] days gestation)

As part of their review of this efficacy supplement, the [redacted] ([redacted] consulted the [redacted] ([redacted] to review the FDA Adverse Event Reporting System (FAERS) for reports of uterine rupture with mifepristone, misoprostol, or both, with special interest in cases occurring in women ≤ 10 weeks pregnant (≤ 70 days).

During the planning stages for this consult, [redacted] conducted a preliminary literature search and identified 43 published case reports that could potentially be applicable to this review. Based on this finding, [redacted] was contacted to determine if a discussion of the literature cases, not also reported in FAERS, should be included as part of this review. [redacted] requested that [redacted] focus our analysis on FAERS cases, while the [redacted] clinical reviewers would conduct the necessary literature review. Therefore, this review is solely focused on FAERS reports, some of which may also be reported in the literature.

1.1 BACKGROUND

Uterine rupture is a rare, life-threatening pregnancy complication for both the mother and the fetus.[1] Common signs and symptoms of uterine rupture include uterine tenderness, abdominal pain, peritoneal irritation, loss of fetal station, vaginal bleeding, shock, and fetal heart rate changes (e.g. bradycardia), or fetal death.[1]

The incidence of rupture in an unscarred uterus versus a scarred uterus is 0.7 and 5.1 per 10,000 deliveries, respectively.[2] The etiology of uterine rupture in an unscarred uterus has been attributed to inherent or acquired weakness of the myometrium, abnormal architecture of the uterine cavity, and disorders of the collagen matrix.[2] Women with a prior cesarean delivery (c-section) or prior transmyometrial uterine surgery would fit the criteria of having a scarred uterus.[1]

Potential contributing risk factors for uterine rupture in both a scarred and unscarred uterus have been identified and include the following: grand multiparity, advancing maternal age, macrosomia, multiple gestation, dystocia resulting in protracted labor, abnormal placentation, a short inter-pregnancy interval, obstetrical procedures (such as breech extraction, uterine instrumentation, cephalic version, dilation and curettage (D&C)), abdominal trauma, and a trial of labor after previous c-section, among others. Medical induction or augmentation of labor with uterotonic medications is also a risk factor for uterine rupture. The presence of several risk factors likely exacerbates the risk of uterine rupture.[1,2,3,4]

For the purposes of this review, the following American College of Obstetricians and Gynecologists (ACOG) definitions were utilized:[5,6]

- Advanced maternal age: age > 35 years old
- 1st trimester: up to and including 13 6/7 weeks of gestation
- 2nd trimester: 14 0/7 weeks to 27 6/7 weeks of gestation
- 3rd trimester: 28 0/7 weeks of gestation and above

1.2 REGULATORY HISTORY

Mifeprex (mifepristone) is a progestin antagonist approved by the FDA on September 28, 2000, indicated for the medical termination of intrauterine pregnancy through 49 days gestation.[7] Mifepristone is used in a regimen with misoprostol for termination of pregnancy. Mifepristone 600 mg orally is administered on day 1, followed by misoprostol 400 mcg orally 48 hours later.

Cytotec (misoprostol) is a synthetic prostaglandin E_1 analogue approved by the FDA on December 27, 1988, that is indicated for reducing the risk of nonsteroidal anti-inflammatory drug-induced gastric ulcers in patients at high risk of complications from gastric ulcers, as well as patients at high risk of developing gastric ulceration.[8] Misoprostol has been used since 1992 under close medical supervision for various obstetrical off-label indications, such as medical termination of pregnancy, cervical ripening, and induction of labor.[9,10] In 2002, labeling was updated to include the addition of a *Labor and Delivery* subsection to the PRECAUTIONS section of the Cytotec package insert.[11]

1.3 PRODUCT LABELING

The current labeling for mifepristone does not contain any information regarding uterine rupture. The applicable sections from the misoprostol[8] label are provided below.

> **BOXED WARNING:**
> CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE BIRTH DEFECTS, ABORTION, OR PREMATURE BIRTH. UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (see also **PRECAUTIONS** and **LABOR AND DELIVERY**).
>
> **PRECAUTIONS:**

Labor and delivery: Cytotec can induce or augment uterine contractions. Vaginal administration of Cytotec, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of Cytotec is uterine tachysystole which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism and lead to adverse fetal heart changes. Uterine activity and fetal status should be monitored by trained obstetrical personnel in a hospital setting.

The risk of uterine rupture increases with advancing gestational ages and prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The use of Cytotec outside of its approved indication may also be associated with meconium passage, meconium staining of amniotic fluid, and Cesarean delivery. Maternal shock, maternal death, fetal bradycardia, and fetal death have also been reported with the use of misoprostol.

Cytotec should not be used in the third trimester in women with a history of Cesarean section or major uterine surgery because of an increased risk of uterine rupture. Cytotec should not be used in cases where uterotonic drugs are generally contraindicated or where hyperstimulation of the uterus is considered inappropriate, such as cephalopelvic disproportion, grand multiparity, hypertonic or hyperactive uterine patterns, or fetal distress where delivery is not imminent, or when surgical intervention is more appropriate.

PATIENT INFORMATION:
Cytotec has been reported to cause the uterus to rupture (tear) when given after the eighth week of pregnancy. Rupture (tearing) of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Cases were included if uterine rupture was reported with the use of mifepristone alone, misoprostol alone, or both.

2.2 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	October 15, 2015
Time Period of Search	January 1, 1965† - October 15, 2015
Search Type	Quick Query

Table 1. FAERS Search Strategy*	
Product Terms	Active Ingredient: Mifepristone; Misoprostol
MedDRA Search Terms (Version 18.0)	Uterine rupture (PT)
* See Appendix A for a description of the FAERS database. † Initiation of FAERS data.	

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 97 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 80 cases were included in the case series of uterine rupture reported with mifepristone use alone, misoprostol use alone, or both (see Figure 1).

Figure 1. FAERS Case Selection

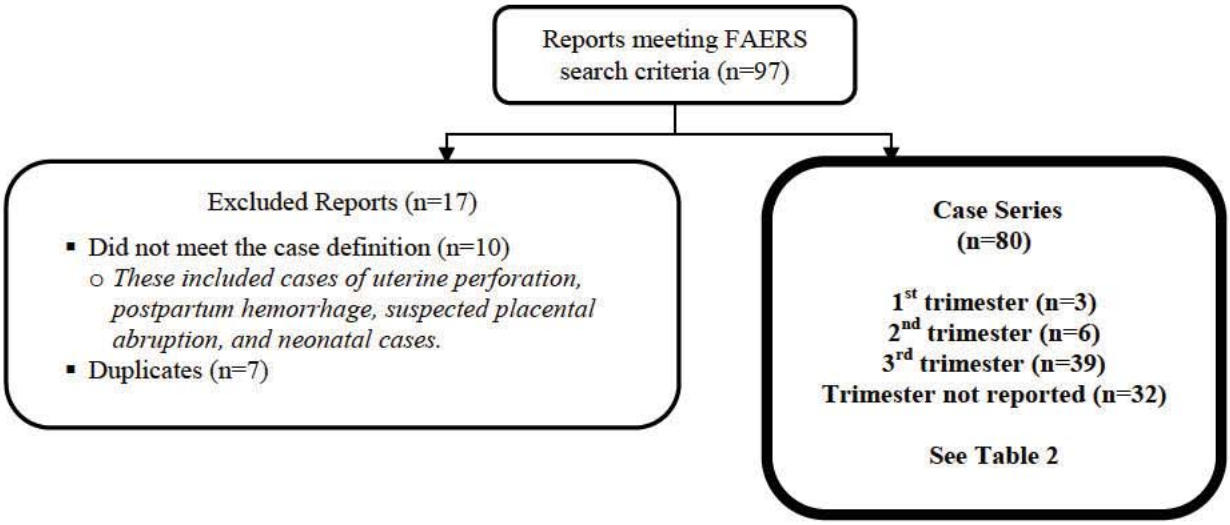

Table 2 summarizes the 80 FAERS cases of uterine rupture reported with mifepristone, misoprostol, or both, for this case series.

Appendix B lists all the FAERS case numbers, FAERS version numbers, FAERS case summaries, and Manufacturer Control numbers for the 80 cases in this case series.

Table 2. Descriptive characteristics of uterine rupture reported with mifepristone use, misoprostol use, or both, to FAERS received by FDA from January 1, 1965, to October 15, 2015 (n=80)

	1st Trimester (n=3)		2nd Trimester (n=6)	3rd Trimester (n=39)	Trimester Not Reported (n=32)
	≤ 10 weeks (n=2)	11 to 13 6/7 weeks (n=1)	14 to 27 6/7 weeks	≥ 28 0/7 weeks	
Age (years)	Mean: 36 Median: 36 Range: 36 Not reported: 1	Mean: 39 Median: 39 Range: 39 Not reported: 0	Mean: 30.8 Median: 27 Range: 26 - 39 Not reported: 0	Mean: 32.6 Median: 32.5 Range: 23 - 41 Not reported: 5	Mean: 31.7 Median: 32 Range: 22 - 28 Not reported: 15
Country	United States: 0 Foreign: 2	United States: 0 Foreign: 1	United States: 0 Foreign: 6	United States: 27 Foreign: 12	United States: 27 Foreign: 5
Report type	Expedited: 2 Direct: 0 Periodic: 0	Expedited: 1 Direct: 0 Periodic: 0	Expedited: 6 Direct: 0 Periodic: 0	Expedited: 23 Direct: 10 Periodic: 6	Expedited: 15 Direct: 10 Periodic: 7
Serious Outcomes* (n=78)	Death: 0 Life-threatening: 0 Hospitalization: 0 Disability: 0 Congenital anomaly: 0 Other serious: 2	Death: 0 Life-threatening: 0 Hospitalization: 1 Disability: 0 Congenital anomaly: 0 Other serious: 1	Death: 0 Life-threatening: 2 Hospitalization: 5 Disability: 2 Congenital anomaly: 0 Other serious: 2	Death: 6 Life-threatening: 6 Hospitalization: 20 Disability: 4 Congenital anomaly: 2 Other serious: 28	Death: 6 Life-threatening: 10 Hospitalization: 17 Disability: 2 Congenital anomaly: 0 Other serious: 16
Year of Receipt by FDA	2000: 1 2008: 1	2008: 1	1996: 1 1997: 1 1999: 1 2003: 1 2007: 1 2011: 1	1997: 1 1998: 4 1999: 4 2000: 13 2001: 1 2002: 2 2003: 3 2004: 2 2006: 1 2008: 1 2009: 1 2010: 3 2011: 1 2013: 1 2014: 1	1994: 2 1997: 3 1999: 1 2000: 6 2001: 3 2002: 2 2003: 3 2004: 3 2005: 2 2006: 1 2007: 1 2008: 1 2011: 2 2012: 2
Medication of Interest Used	Mifepristone: 0 Misoprostol: 2 Both: 0	Mifepristone: 0 Misoprostol: 0 Both: 1	Mifepristone: 0 Misoprostol: 4 Both: 2	Mifepristone: 0 Misoprostol: 39 Both: 0	Mifepristone: 0 Misoprostol: 32 Both: 0

Table 2. Descriptive characteristics of uterine rupture reported with mifepristone use, misoprostol use, or both, to FAERS received by FDA from January 1, 1965, to October 15, 2015 (n=80)					
	1st Trimester (n=3)		2nd Trimester (n=6)	3rd Trimester (n=39)	Trimester Not Reported (n=32)
	≤ 10 weeks (n=2)	11 to 13 6/7 weeks (n=1)	14 to 27 6/7 weeks	≥ 28 0/7 weeks	
Route Misoprostol Administered	Vaginal: 1 Not reported: 1	Oral and vaginal: 1	Oral: 1 Vaginal: 3 Oral and vaginal: 1 Not reported: 1	Oral: 3 Vaginal: 32 Not reported: 4	Oral: 1 Vaginal: 15 Not reported: 16
Reported Indication^	Pregnancy termination: 2	Pregnancy termination: 1	Induction of labor: 1 Pregnancy termination: 5	Cervical ripening: 11 Induction of labor: 38 Not reported: 1	Cervical ripening: 1 Induction of labor: 26 Pregnancy termination: 4 Not reported: 2
Weeks of Gestation	5 weeks: 1 8 2/7 weeks: 1	12 weeks: 1	16 5/7 weeks: 1 17 weeks: 1 18 weeks: 1 19 weeks: 1 20 weeks: 2	30 weeks: 1 "8 month" old fetus: 1 35 - 35 6/7 weeks: 2 36 6/7 weeks: 1 37 - 37 6/7 weeks: 2 "37 - 38" weeks: 1 38 - 38 6/7 weeks: 7 39 - 39 6/7 weeks: 7 ≥ 40 weeks: 15 "Term" pregnancy: 1 "Post-date" pregnancy: 1	Not applicable
Additional Labor-Inducing/ Supporting Medications†	None Reported	None Reported	**(n=1)** Gemeprost: 1 Oxytocin: 1	**(n=15)** Dinoprostone: 1 Oxytocin: 14	**(n=7)** Dinoprostone: 2 Oxytocin: 6

Table 2. Descriptive characteristics of uterine rupture reported with mifepristone use, misoprostol use, or both, to FAERS received by FDA from January 1, 1965, to October 15, 2015 (n=80)

	1st Trimester (n=3)		2nd Trimester (n=6)	3rd Trimester (n=39)	Trimester Not Reported (n=32)
	≤ 10 weeks (n=2)	11 to 13 6/7 weeks (n=1)	14 to 27 6/7 weeks	≥ 28 0/7 weeks	
Other Reported Potential Risk Factors for Uterine Rupture‡	**(n=1)** Advanced maternal age: 1 Previous c-section: 1	**(n=1)** Advanced maternal age: 1	**(n=5)** Additional uterotonics: 1 Advanced maternal age: 2 Cervical fibrosis: 1 Previous c-section(s): 3 Previous D&C(s): 2	**(n=34)** Additional uterotonics: 15 Advanced maternal age: 8 "Difficult previous birth:" 1 Dystocia: 2 Grand multiparity: 2 Macrosomia: 3 Placenta accreta: 1 Previous c-section(s): 11 Previous D&C(s): 5 Previous uterine perforation: 1 Short inter-pregnancy interval: 1 Version: 1	**(n=17)** Additional uterotonics: 7 Advanced maternal age: 3 Grand multiparity: 1 Macrosomia: 2 Placental abruption: 1 Previous c-section(s): 8
Published Case Report/ Literature Reported in FAERS	Yes: 1	Yes: 0	Yes: 3	Yes: 14	Yes: 7

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A case may contain more than one serious outcome.
^ A case may contain more than one indication.
† A case may contain more than one additional labor-inducing/supporting medication.
‡ A case may contain more than one other potential risk factor for uterine rupture.

Cases of uterine rupture reported with mifepristone, misoprostol, or both, at less than or equal to 10 weeks gestation (≤ 70 days) are further summarized below.

FAERS Case # 6535634, Foreign (France), Outcome - Other Serious (2008)
A pregnant female (age unknown) received an unknown dose and route of misoprostol for the termination of pregnancy on an unspecified date. On an unknown date, the patient felt "unwell" and went to the hospital. An ultrasound was completed which showed that the pregnancy was still ongoing and that there was "an important uterine separation." The patient was noted to be at week 5 of amenorrhea.

Reviewer's Comments: This case describes "an important uterine separation" that was MedDRA coded as a uterine rupture after misoprostol use only for termination of pregnancy in a patient that was approximately 5 weeks pregnant. The lack of information and clinical details provided with this case prevents a thorough and complete assessment of this case.

FAERS Case # 3493578, Foreign (United Kingdom), Outcome - Other Serious (2000)
A 36-year-old (gravida 3, para 2; one delivery via c-section and one vaginal delivery) female was admitted to the hospital and received misoprostol 800 mcg vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was noted to be 8 weeks and 2 days pregnant. Approximately 2.5 hours after misoprostol insertion, the patient experienced severe lower abdominal pain and vaginal bleeding. She was then examined while under anesthesia, and bleeding was documented as profuse and consistent with rupture of the uterus. A laparotomy was performed when it was found that the uterine scar had ruptured with division of both uterine arteries. The patient received two units of blood and a subtotal hysterectomy was performed. Her post-operative recovery was uneventful.

Reviewer's Comments: This published case report[12] describes uterine rupture approximately 2.5 hours after vaginal misoprostol insertion. The potential risk factors identified for uterine rupture include advanced maternal age and a previous c-section.

4 DISCUSSION

The FAERS search retrieved a total of 80 cases of uterine rupture, with 77 citing misoprostol use alone, zero cases citing mifepristone use alone, and three cases citing mifepristone and misoprostol use in conjunction. Vaginal administration of misoprostol was documented in 53 of the 80 cases, including two cases noting both oral and vaginal misoprostol administration; 22 cases did not report the route of administration. The remaining five cases noted only oral administration of misoprostol. Twenty-five of the 80 FAERS cases originated in the published medical literature.

In addition to mifepristone and misoprostol exposure, (b) (6) assessed the FAERS cases for other risk factors that could contribute to uterine rupture. Fifty-eight cases noted at least one additional potential risk factor. The predominant risk factors reported included a history of at least one previous c-section (n=23), or the use of additional uterotonic drugs (n=23), such as oxytocin and dinoprostone. Nine of the 23 cases that documented the use of additional uterotonic drugs had at least one previous c-section, which would likely further increase the risk of uterine rupture independent of the risk associated with the use of additional uterotonic drugs.

(b) (6) also evaluated FAERS cases of uterine rupture by trimester. Thirty-two of the 39 cases of uterine rupture identified during the 3rd trimester noted vaginal misoprostol use. Eleven of the 39 cases in the 3rd trimester also documented the use of misoprostol for the induction of labor, cervical ripening, or both, in women that had at least one previous c-section. This is an important observation because both the current misoprostol labeling and the ACOG Practice Bulletin for the Induction of Labor recommend the avoidance of misoprostol in the 3rd trimester of pregnancy in women with a prior c-section or history of a major uterine surgery, as these women are believed to be at increased risk for uterine rupture.[8,13]

The majority of the FAERS cases either occurred in the 3rd trimester of pregnancy (39/80; 48.8%), or did not report gestational age (32/80; 40%). In the cases where the gestational age was not reported, it is likely that most of these cases occurred during the 2nd or 3rd trimester as 26 of these 32 cases noted induction of labor as the reason for misoprostol use. Two of the 80 cases (2.5%) reported uterine rupture within the first 10 weeks of pregnancy; however, if the cases without gestation age are not included as 2nd or 3rd trimester exposures despite the noted indication of labor induction, the percentage increases to approximately 4% (2 out of 48 cases where the gestation age is provided). Regardless of the approach, uterine rupture associated with the use of mifepristone alone, misoprostol alone, or both, is likely a rare event, especially in the 1st trimester of pregnancy.

Two cases of uterine rupture were reported within the first 10 weeks of pregnancy. In both cases, misoprostol alone was utilized for termination of pregnancy. The first case, as described in Section 3.1, provided minimal information other than documentation of a 5 week gestation, and an ultrasound noting "an important uterine separation" during an unspecified time after misoprostol administration. The dose and route of misoprostol, in addition to any relevant information regarding the pregnant female (such as age, gravida, and medical history), was not provided. The remaining case was a published case report[12] in which uterine rupture was documented as occurring approximately 2.5 hours after 800 mcg of misoprostol was administered vaginally for cervical preparation prior to surgical termination of pregnancy. The patient was noted to be 8 weeks and 2 days pregnant, had a history of a prior c-section, and was of advanced maternal age.

5 CONCLUSION

In conclusion, a review of the FAERS cases did identify cases of uterine rupture with the use of misoprostol alone, and with the use of mifepristone in combination with misoprostol. No cases of uterine rupture were reported with mifepristone alone. While two cases of uterine rupture with misoprostol for the termination of pregnancy were reported in the ≤ 10 weeks gestation group, the vast majority of the cases documented the occurrence of uterine rupture in the 3rd trimester of pregnancy with vaginal misoprostol use alone for the induction of labor.

6 REFERENCES

[1] Kilpatrick CC, Orejuela FJ. Approach to abdominal pain and the acute abdomen in pregnant and postpartum women. In: UpToDate. Ramin SM, Weiser M (Ed). UpToDate, Waltham, MA. (Accessed October 27, 2015)

[2] Smith JF, Wax JR. Rupture of the unscarred uterus. In: UpToDate. Lockwood, CJ (Ed). UpToDate, Waltham, MA. (Accessed October 27, 2015)

[3] Ofir K, Sheiner E, Levy A, Katz M, Mazor M. Uterine rupture: differences between a scarred and an unscarred uterus. Am J Obstet Gynecol. 2004 Aug;191(2):425-9.

[4] Smith JG, Mertz HL, Merrill DC. Identifying risk factors for uterine rupture. Clin Perinatol. 2008 Mar;35(1):85-99.

[5] The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 102: Management of Stillbirth. Obstet Gynecol. 2009 Mar;113(3):748-61.

[6] The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) Committee Opinion No. 611: Method for Estimating Due Date. Obstet Gynecol. 2014 Oct;124(4):863-6.

[7] Mifeprex (mifepristone) [Package Insert]. New York, NY: Danco Laboratories, LLC; April 22, 2009.

[8] Cytotec (misoprostol) [Package Insert]. New York, NY: GD Searle, LLC; November 2012.

[9] Thomas A, Jophy R, Maskhar A, Thomas RK. Uterine rupture in a primigravida with misoprostol used for induction of labour. BJOG. 2003 Feb;110(2):217-8.

[10] Ezegwui HU. Uterine rupture in a primigravida when misoprostol was used for induction of labour and subsequent successful pregnancy outcome. J Obstet Gynaecol. 2006 Feb;26(2):160-1.

[11] Cytotec (misoprostol) [Package Insert]. New York, NY: GD Searle, LLC; April 2002.

[12] Jwarah E, Greenhalf JO. Rupture of the uterus after 800 micrograms misoprostol given vaginally for termination of pregnancy. BJOG. 2000 Jun;107(6):807.

[13] The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 107: Induction of Labor. Obstet Gynecol. 2009 Aug;114(2 Pt 1):386-97.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, FAERS CASE SUMMARY INFORMATION, AND MANUFACTURER CONTROL NUMBERS

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
6535634	FR-PFIZER INC-2008004891	1	1/25/2008	NR	Miso	None	Medical abortion	5 wks	Previous medical history is unknown	
3493578	000619-SK110	1	6/30/2000	36	Miso	None	Termination of pregnancy	8 and 2/7 wks	Previous c-section; advanced maternal age	Y (British Jour of OB GYN; June 2000; 107; 807)
6826056	GB-PFIZER INC-2008100689	1	11/30/2008	39	Both	None	Medical abortion	12 wks	Advanced maternal age	
8087646	GB-MYLANLABS-2011S1015775	1	8/12/2011	27	Miso	None	Induction of labor for intrauterine fetal demise	16 and 5/7 wks	Two previous d&c; Cervical fibrosis secondary to two previous large loop excisions of transformation zone (LLETZ) for cervical intraepithelial neoplasm	Y (Jour OB GYN; 2009 Jul; 29(5); 443)
4018081	2003174735 DK	1	10/8/2003	27	Miso	None	Induce abortion	17 wks	Previous c-section	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
5486636	961023SK024	1	11/13/1996	26	Both	None	Termination of pregnancy	18 wks	None reported	Y (Europ J OB GYN and Repro Biol; 1996; 65; 175-176)
3380136	B0072245A	1	10/27/1999	39	Miso	None	Medical abortion	19 wks	Advanced maternal age	
5568168	970529SK651	1	6/9/1997	27	Miso	None	Induce abortion	20 wks	Previous c-section	
6213047	PHBS2007GB00484	1	1/11/2007	39	Both	Gemeprost and oxytocin	Termination of pregnancy	20 wks	2 previous c-sections; use of additional uterotonic agents (other than miso); advanced maternal age; previous d&c	Y (Jour OB GYN; 2006; 26(8); 827-828)
9562028	IE-PFIZER INC-2013276197	1	9/27/2013	32	Miso	None	Induction of labor for intrauterine fetal demise	30 wks	"Previous difficult birth"	
10538160	KR-PFIZER INC-2014289438	1	10/23/2014	38	Miso	None	Induction of labor for intrauterine fetal demise	"8 month old fetus"	Advanced maternal age	
3200342	990126-SK156	1	1/29/1999	27	Miso	Oxytocin	Induction of labor secondary to severe preeclampsia	35 wks	Previous d&c; use of additional uterotonic agents (other than miso)	Y (Jour OB GYN; 1998; 18(2); 184-185)

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
3202143	990125-SK821	1	1/29/1999	39	Miso	None	Induction of labor for IUGR and oligohydramnios	35 and 5/7 wks	Previous c-section; advanced maternal age	Y (OB GYN; 1998; 91(5); 828-830)
7676227	FR-PFIZER INC-2010148739	3	11/19/2010	27	Miso	None	Induction of labor for IUGR	36 and 6/7 wks	None reported	
3446021	000303-SK968	1	3/16/2000	29	Miso	Oxytocin	Induction of labor secondary to increased blood pressure	37 wks	Previous c-section; use of additional uterotonic agents (other than miso)	Y (Am J OB GYN; 1999; 180(6); 1535-1542)
6865208	DK-PFIZER INC-2008154818	4	12/23/2008	30	Miso	None	Induction of labor secondary to severe preeclampsia	37 and 5/7 wks	None reported	
3658225	Direct Report	1	5/21/2001	37	Miso	None	Cervical ripening; induction of labor	37-38 wks	Advanced maternal age	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
3446028	000303-SK967	1	3/16/2000	27	Miso	Oxytocin	Induction of labor secondary to maternal insulin-dependent diabetes	38 wks	Previous c-section; use of additional uterotonic agents (other than miso)	Y (Am J OB GYN; 1999; 180(6); 1535-1542)
3570614	Direct Report	1	11/14/2000	30	Miso	Oxytocin	Cervical ripening; Induction of labor	38 wks	Dystocia; use of additional uterotonic agents (other than miso)	
3411436	991217-SK980	2	12/23/1999	38	Miso	None	NR	38 wks	Previous uterine perforation; advanced maternal age	
3925994	2002109666 US	1	2/26/2003	38	Miso	Oxytocin	Induction of labor for decreased AFI and oligohydramnios	38 wks	Use of additional uterotonic agents (other than miso); advanced maternal age	
4011614	Direct Report	1	9/26/2003	41	Miso	None	Cervical ripening; Induction of labor	38 wks	Advanced maternal age	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
3211435	990209-SK266	1	2/12/1999	NR	Miso	None	Induction of labor	38 wks	None reported	Y (Rev OB SYN Venez; 1996; 56(2); 67-74)
3121525	Direct Report	1	1/14/1998	26	Miso	None	Induction of labor for intrauterine fetal demise	38 and 4/7 wks	Previous c-section	
5603262	970714SK994	1	7/30/1997	34	Miso	None	Induction of labor	39 wks	Previous d&c	Y (OB GYN; 1997; 89; 832-833)
3446030	000303-SK965	1	3/16/2000	36	Miso	None	Induction of labor secondary to suspected macrosomia	39 wks	2 previous c-sections; version for breech presentation; advanced maternal age; macrosomia	Y (Am J OB GYN; 1999; 180(6); 1535-1542)
3915893	000308-SK959	1	3/16/2000	39	Miso	None	Induction of labor for HTN and fetal macrosomia	39 wks	Macrosomia; advanced maternal age	Y (Am J OB GYN; 1999; 180(6): 1551-1559)
3925984	2002104324 US	1	2/26/2003	NR	Miso	Oxytocin	Cervical ripening; Induction of labor	39 wks	Previous c-section; use of additional uterotonic agents (other than miso)	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
3141208	980114-SK162	2	3/9/1998	29	Miso	None	Cervical ripening; Induction of labor	39 and 2/7 wks	Previous c-section	
3537973	Direct Report	1	9/15/2000	33	Miso	Oxytocin	Induction of labor	39 and 3/7 wks	Grand multiparity; use of additional uterotonic agents (other than miso)	
3446032	000302-SK676	1	3/16/2000	26	Miso	Oxytocin	Induction of labor for maternal exhaustion	39 and 6/7 wks	Previous c-section; use of additional uterotonic agents (other than miso)	Y (Am J OB GYN; 1999; 180(6); 1535-1542)
3467539	000414-SK112	1	5/1/2000	26	Miso	None	Induction of labor	40 wks	Placenta accreta	Y (GYN OB Invest; 1995; 39; 252-256)
3122956	980114-SK161	2	3/9/1998	34	Miso	Oxytocin	Cervical ripening; Induction of labor	40 wks	Dystocia; macrosomia; previous d&c; use of additional uterotonic agents (other than miso)	
5664281	2003188525 US	2	2/17/2004	39	Miso	Oxytocin	Induction of labor	40 wks	Use of additional uterotonic agents (other than miso); advanced maternal age	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
3462541	000405-SK976	1	4/19/2000	NR	Miso	None	Induction of labor	40 wks	Previous d&c	Y (Inter Jour GYN OB; 2000; 68; 43-44)
3117476	980407-SK060	2	4/20/1998	26	Miso	None	Cervical ripening; Induction of labor	40 and 2/7 wks	2 previous c-sections	Y (Aus NZ Jour of OB GYN; 1998; 38(1); 96-97)
4105985	2003184165 US	3	2/17/2004	30	Miso	Oxytocin	Cervical ripening; Induction of labor	40 and 2/7 wks	Use of additional uterotonic agents (other than miso)	
7684419	CH-PFIZER INC-2010157837	1	11/29/2010	36	Miso	None	Induction of labor	40 and 2/7 wks	Advanced maternal age	
3493157	000614-SK250	1	6/28/2000	39	Miso	None	Induction of labor	40 and 5/7 wks	Advanced maternal age	Y (Med Sci Law; 2000; 40(1); 78-82)
7634883	2009305062	1	9/14/2010	NR	Miso	None	Induction of labor	"Term"	None reported	
3446008	000308-SK953	1	3/16/2000	28	Miso	Oxytocin	Cervical ripening; Induction of labor	41 wks	2 previous c-sections; use of additional uterotonic agents (other than miso)	Y (Am J OB GYN; 1999; 180(6): 1551-1559)

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
6186170	2005151336	1	9/6/2006	35	Miso	Dinoprostone	Induction of labor	41 wks	Use of additional uterotonic agents (other than miso)	
3453012	Direct Report	1	3/8/2000	29	Miso	Oxytocin	Cervical ripening; Induction of labor	41 and 3/7 wks	Use of additional uterotonic agents (other than miso)	
3553045	Direct Report	1	10/12/2000	32	Miso	None	Induction of labor	41 and 3/7 wks	Grand multiparity; use of additional uterotonic agents (other than miso)	
8272366	Direct Report	1	12/2/2011	NR	Miso	Oxytocin	Induction of labor	41 and 3/7 wks	Use of additional uterotonic agents (other than miso)	
3788743	Direct Report	1	4/25/2002	23	Miso	None	Cervical ripening; Induction of labor	41 and 5/7 wks	Previous c-section; short inter-pregnancy interval (~ 6 months)	
6880865	DE-PFIZER INC-2008159489	8	1/14/2009	39	Miso	None	Induction of labor	42 and 3/7 wks	Advanced maternal age; previous d&c	
3788274	Direct Report	1	4/26/2002	37	Miso	None	Induction of labor	"Post-date pregnancy"	Advanced maternal age	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
6825783	NO-PFIZER INC-2008099230	1	11/28/2008	31	Miso	None	Induce abortion	NR	Previous c-section	
3043704	Direct Report	1	12/4/1997	35	Miso	None	Cervical ripening; Induction of labor	NR	Previous c-section	
8145841	GB-PFIZER INC-2011219642	3	9/21/2011	NR	Miso	None	Induction of labor for intrauterine fetal demise	NR	Previous medical history is unknown	
3201694	990126-SK155	1	1/29/1999	22	Miso	Oxytocin	Induction of labor secondary to eclampsia	NR	Use of additional uterotonic agents (other than miso)	Y (Jour OB GYN; 1998; 18(2); 184-185)
7954530	Direct Report	1	5/11/2011	23	Miso	Dinoprostone and oxytocin	Induction of labor	NR	Use of additional uterotonic agents (other than miso)	
8760330	Direct Report	1	8/29/2012	26	Miso	None	Induction of labor	NR	None reported	
6029647	Direct Report	1	4/11/2006	29	Miso	None	Induction of labor	NR	None reported	
4057550	Direct Report	1	1/7/2004	30	Miso	None	Induction of labor	NR	Previous c-section	
3627852	Direct Report	1	3/22/2001	31	Miso	None	Induction of labor	NR	Previous c-section; placental abruption	

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
5802880	Direct Report	1	5/16/2005	31	Miso	None	Induction of labor	NR	None reported	
3759724	2002090200 US	2	1/30/2002	32	Miso	None	Induction of labor	NR	None reported	
8763266	Direct Report	1	8/31/2012	32	Miso	None	Induction of labor	NR	Macrosomia	
3594580	2001039782 US	2	1/16/2001	35	Miso	None	Induction of labor	NR	Grand multiparity	
3780336	Direct Report	1	4/8/2002	35	Miso	None	Induction of labor	NR	None reported	
3925979	2002101539 US	1	2/26/2003	35	Miso	None	Induction of labor	NR	Macrosomia	
6355128	Direct Report	1	7/5/2007	36	Miso	None	Induction of labor	NR	Advanced maternal age	
3506245	000713-SK605	1	7/26/2000	38	Miso	Oxytocin	Induction of labor	NR	Previous c-section; advanced maternal age; use of additional uterotonic agents (other than miso)	
3613899	2001044857 US	1	2/26/2001	38	Miso	None	Induction of labor	NR	Advanced maternal age	
3446011	000303-SK976	1	3/16/2000	NR	Miso	Oxytocin	Induction of labor	NR	Previous c-section; use of additional uterotonic agents (other than miso)	Y (Am J OB GYN; 1999; 180(6): 1535-1542)

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
3446014	000303-SK975	1	3/16/2000	NR	Miso	None	Induction of labor	NR	Previous c-section	Y (Am J OB GYN; 1999; 180(6); 1535-1542)
3446016	000303-SK972	1	3/16/2000	NR	Miso	Oxytocin	Induction of labor	NR	Previous c-section; use of additional uterotonic agents (other than miso)	Y (Am J OB GYN; 1999; 180(6); 1535-1542)
3564654	001023-SK184	1	11/3/2000	NR	Miso	None	Induction of labor	NR	None reported	
3915894	000317-SK642	1	3/24/2000	NR	Miso	None	Induction of labor	NR	None reported	Y (Am J OB GYN; 1997; 177(2); 364-371)
3925983	2002104322 US	1	2/26/2003	NR	Miso	None	Induction of labor	NR	None reported	
4000087	2003174061 US	1	8/29/2003	NR	Miso	Oxytocin	Induction of labor	NR	Use of additional uterotonic agents (other than miso)	
4105973	2003151832 US	1	2/17/2004	NR	Miso	None	NR	NR	None reported	
4220701	2004192837 US	1	9/3/2004	NR	Miso	None	Induction of labor	NR	None reported	
5149230	940804SK736	1	8/17/1994	NR	Miso	None	Induce abortion	NR	None reported	Y (Contraception; 1994 Feb; 49(2): 101-110)

FAERS Case #	MFR Ctrl #	Version #	FDA Initial Rec'd Date	Maternal Age in Years	Miso, Mife, or Both	Additional labor-inducing/ supporting meds	Indication	Pregnancy GA	Other potential risk factors for rupture	Published case report/literature and reference information
5149248	940804SK735	1	8/17/1994	NR	Miso	None	Induce abortion	NR	None reported	Y (Contraception; 1994 Feb; 49(2): 101-110)
5539644	961022SK850	1	2/4/1997	NR	Miso	None	Induction of labor	NR	None reported	
5539696	961022SK848	1	2/4/1997	NR	Miso	Dinoprostone	Induce abortion	NR	Use of additional uterotonic agents (other than miso)	
5877301	2004229454 US	1	9/9/2005	NR	Miso	None	NR	NR	None reported	

Abbreviations: Mife = Mifepristone; Miso = Misoprostol; GA = Gestation Age; Wks = Weeks; D&C = Dilation and Curettage; Y = Yes

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

11/16/2015

(b) (6)

11/16/2015

(b) (6)

11/17/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 20687 BLA#	NDA Supplement #: S- 020 BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☒ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Mifeprex Established/Proper Name: mifepristone Dosage Form: tablet Strengths: 200 mg		
Applicant: Danco Laboratories, LLC Agent for Applicant (if applicable):		
Date of Application: May 28, 2015 Date of Receipt: May 29, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: March 29, 2016	Action Goal Date (if different):	
Filing Date: July 28, 2015	Date of Filing Meeting: July 10, 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Induction of Abortion		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☒ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify*** (b) (6) ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☒ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☐	☐	☒	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☐	☐	☒	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☐	☐	☒	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients*	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☒		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☒	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

[5] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐		

ATTACHMENT

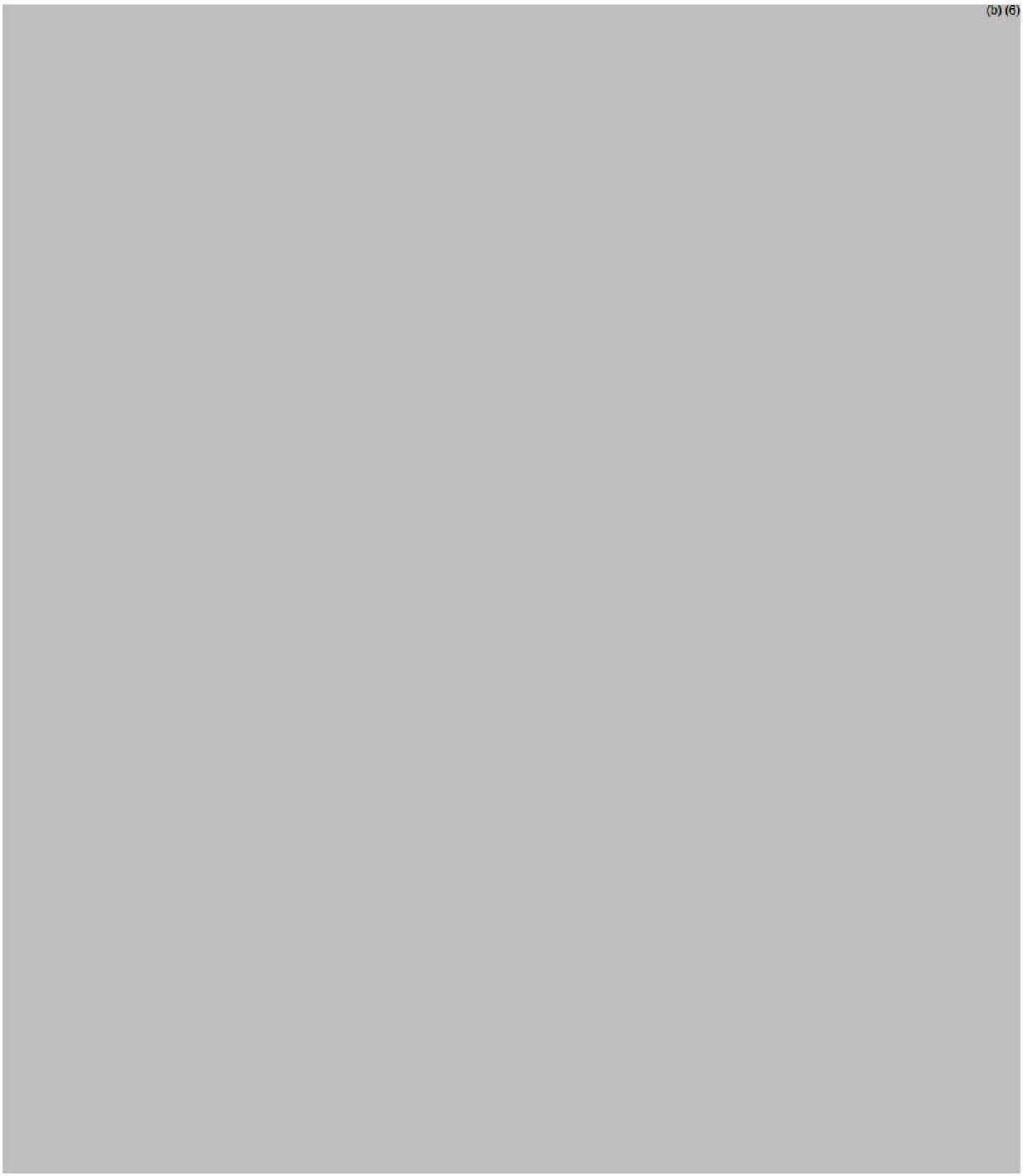
MEMO OF FILING MEETING

DATE:

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names	Present at filing meeting? (Y or N)
(b) (6)		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FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO Drug product used in the clinical trials cited in literature.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: literature review	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☐ YES ☒ NO ☐ YES ☒ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: (b) (6)	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

07/10/2015